IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Raveendra Khandurao Tikare	Examiner: Unknown
Serial No.:	10/719,660	Group Art Unit: 1626
Filed:	November 21, 2003	Docket: 1365.074US1
Title:	STEREOSELECTIVE SYNTHESIS OF 2-HYDROXY-4-PHENYLBUTYRIC ACID ESTERS	

COMMUNICATION REGARDING FILING OF PRIORITY DOCUMENT

Commissioner for Patents
P.O.Box 1450
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In accordance with the requirements for claiming right of priority under 35 U.S.C. 119, enclosed for filing in connection with the above-identified application is a certified copy of Applicant's prior application, United Kingdom Patent Application No. 0112322.3, filed May 21, 2001.

Respectfully submitted,

RAVEENDRA KHANDURAO TIKARE

By his Representatives,

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Date December 19, 2004 By William F Prout

William F Prout
Reg. No. 33,995

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PATRICIA A. HULTMAN
Name

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The Patent Office
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Patents Form 1/77

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Cardiff Road
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1. Your reference — PA 4107

0112322.3

... ... you fill in this part)

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Fermenta Biotech Ltd
C/o Duphar-Interfran Ltd
Opp. Vidyapeeth, S.V. Road
Majiwada
Thane-400 607
India

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation — India

81 508 560 8

4. Title of the invention — SYNTHESIS OF CHIRAL INTERMEDIATES

5. Name of your agent *(if you have one)* — SOMMERVILLE & RUSHTON

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

46 Grosvenor Road
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Herts AL1 3AW

Patents ADP number *(if you know it)* — 1511001 ✓

Marks & Clerk
Welligton House
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CB1 1RT 4271125003

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6/8/03
JG

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
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YES

Patents Form 1/77

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Continuation sheets of this form	
Description	6
Claim(s)	2
Abstract	1
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Priority documents	0
Translations of priority documents	0
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	0
Request for preliminary examination and search *(Patents Form 9/77)*	9
Request for substantive examination *(Patents Form 10/77)*	10
Any other documents *(please specify)*	0

11. I/We request the grant of a patent on the basis of this application.

Signature: Sommerville & Rushton

Date: 21 May 2001

12. Name and daytime telephone number of person to contact in the United Kingdom: Dr Ian H Coates 01727 854215

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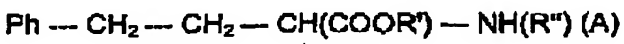
SYNTHESIS OF CHIRAL INTERMEDIATES

The present invention relates to a process for the synthesis of chiral compounds, and in particular chiral esters, for use as intermediates in the synthesis of the family of acetylcholine esterase (ACE) inhibitors known as 'prils'.

The 'prils' have the general formula (A):



$$Ph --- CH_2 --- CH_2 — CH(COOR') — NH(R'') \quad (A)$$

wherein R' is hydrogen or C_1-C_2 alkyl and R" is selected from a large number of possible moieties. Examples of 'prils' include lisinopril, cilazapril, enalapril, benazepril, ramipril, delapril, enalaprilat, imidapril, spirapril, trandolapril and others.

These 'pril' compounds are chiral compounds, only one of their diastereomers being pharmacologically active. It is therefore necessary to isolate and purify the active diastereomer, rather using a racemic mixture, for pharmaceutical/medical applications.

Typically, separation of diastereomers is carried out by preferential crystallisation, for example as described in US patent specification no. 5,616,727. However, the yields of such crystallisations are often low and, indeed, the yield from the process used in US patent specification no. 5,616,727 was only 68%.

Alternatively, a stereochemical synthesis may be used, wherein various intermediates used in the preparation of the 'prils' are, in turn, prepared in chiral form, which results in a predominance of the desired diastereomer in the final 'pril' product. However, such chiral syntheses are complex and the yields are also unsatisfactory.

The present invention relates to an improved, stereospecific process for the synthesis of an intermediate for making 'pril' compounds. This intermediate can be

converted to the required 'pril' isomer, or any other desired end-product, without loss of stereospecificity. The intermediate of interest is an ester of formula (I):

$$Ph — CH_2 — CH_2 — CH(OR^2) — COOR^1 \quad (I)$$

wherein * signifies the (R) stereoisomer;
R^1 is selected from C_{1-6} alkyl, preferably ethyl; and
R^2 is hydrogen, a protecting group or a leaving group.

Suitable leaving groups R^2 include p-toluene sulphonyl (tosyl), methane sulphonyl chloride (mesyl), trifluoromethane sulphonyl (triflic), and p-nitrobenzene sulphonyl.

Suitable protecting groups R^2 include *tert*-butyl dimethyl silyl (TBDMS), TMS, BOC and the like.

One method of stereospecific synthesis involves the conversion of the compound (R)-2-hydroxy-4-phenylbutyronitrile having the formula (II):

$$Ph — CH_2 — CH_2 — CH(OH) — CN \quad (II)$$

wherein * signifies the (R) stereoisomer; and Ph is the phenyl group $C_6 H_5$ to the corresponding ester of formula (I).

In Tet. Lets. 30 (15) 1917-20 (1989) is disclosed the above process to produce a compound of formula (I) wherein R^2 is H and R^1 is ethyl. However, the method described involves a three-stage process, resulting in a yield of only 78%, based on the nitrile of formula (II). The three process steps are: (i) treating the nitrile (II) with dihydopyran in pyridinium p-toluene sulphonate to prepare the THP derivative; (ii) hydrolysing the nitrile group with sodium hydroxide; and, finally, treating the resulting acid with anhydrous ethanol and a catalytic amount of concentrated sulphuric acid.

We have therefore looked at the possibility of using alternative methods of synthesising this ester, but none of these appeared to provide the desired combination of high *ee* (*eg* 97-98%); economic reaction time; acceptable yields (*eg* > 80%); and overall ease of handling and commercial viability of the process.

Instead, we have surprisingly found that, by careful selection of novel reaction conditions and reagents, we can obtain the desired *ee* in high yields and under commercially-acceptable conditions, involving a so-called 'one-pot' reaction, in which the reaction appears to go in one step, without the addition of further reagents or reactants, but with the formation of an unstable intermediate that need not be isolated but converts *in situ* to the desired compound of formula (I).

The novel one-pot reaction according to this invention involves reacting the nitrile of formula (II) with an alcoholic solution of an inorganic acid, such as sulphuric acid or hydrochloric acid, to give the ester of formula (I) *via* an *in situ* conversion.

Accordingly, the present invention further provides a process for preparing a compound of formula (I), which process comprises reaction of an intermediate imine of formula (III):

$$[Ph — CH_2 — CH_2 — CH(OR^2) — CH{=}NH.HX] \qquad (III)$$

in which R^2 is as defined in formula (I); and X is the anion of an inorganic acid, such as sulphate or halide, preferably halide, more preferably chloride, with an alcohol of formula R^1OH, in which R^1 is as defined in formula (I).

It is preferred that R^1 is C_1-C_4 alkyl, for example methyl, ethyl, n-propyl, *iso*-propyl, n-butyl, *iso*-butyl or *tert*-butyl. Accordingly, ethanol is the preferred alcohol. Conveniently, the alcoholic solution of the acid is prepared by bubbling dry, gaseous acid into absolute alcohol. Preferable, the solution comprises at least 4-5% w/v of acid (gas), more preferably > 7%w/v, such as in the range of from 7-15% w/v, based on grams of acid per 100ml of alcohol.

It is preferred that the alcohol/acid solution be as anhydrous as possible, in order to ensure that the ester is formed in preference to the corresponding acid. The reaction may be carried out at a temperature in the range of from 0 to 80 °C, such as at reflux temperature of the reaction mixture, at atmospheric pressure. For example, using the ethanol/HCl, the reaction may be carried out at 75-80°C over a period of 15 hours, or for 2 hours at 10-15 °C followed by refluxing for 15 hours, all at

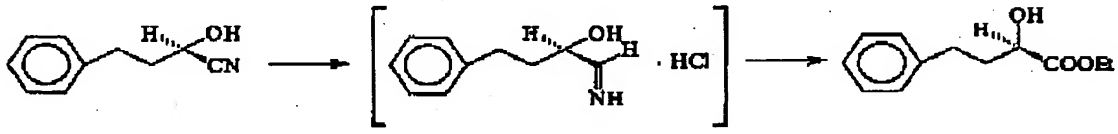
atmospheric pressure. The skilled chemist will be able to adjust the temperature/pressure/reaction period factors appropriately.

The yield of this reaction is about 80% of theoretical with an enantiomeric excess (*ee*), based on optical rotation, of the (R) isomer of about 97%.

The present invention therefore further provides an ester of formula (I) whenever prepared by a process according to this invention; and such a compound (I) for use in, or whenever used in, the preparation of a stereospecific 'pril' of formula (A). Furthermore, there is provided a method for the preparation of a stereospecific 'pril' of formula (A), which method comprises preparation of an ester of formula (I) by a process according to this invention; and a stereospecific 'pril' of formula (A), whenever prepared by such a process.

The invention will now be described in more detail with reference to the following non-limiting examples.

Example: Preparation of (R)-2-Hydroxy-4-phenyl butyric acid



(R)-isomer (R)-isomer

(II) (III) (I)

(a) Preparation of alcoholic HCl (g)

To 1 kg of common salt (NaCl) was added 250 ml of concentrated sulphuric acid, dropwise at room temperature. The hydrogen chloride gas evolved was first passed through a trap containing concentrated sulphuric acid to dry it and then passed with stirring into absolute alcohol (2l) which was kept at 0-5°C. The process was carried out for 4-6 hours until the required strength was obtained.

(b) Preparation of Title Compound

To (R)-2-hydroxy-4-phenyl-butyronitrile ((II), 250g, 1.55 M) was added absolute alcohol (2l) which contained at least 7% w/v of dry hydrogen chloride gas at 10-15°C. The mixture was stirred for 2 hours at the same temperature. This was carried out to allow confirmation of the conversion of the nitrile to the corresponding imine hydrochloride. After this, the reaction mass was refluxed at 75-80°C. The reaction was monitored using TLC and after 15 hours was found to be complete.

The alcohol was removed from the reaction mass *in vacuo* at 55-60°C. The resulting residue was taken in water (1l) and extracted with dichloromethane (500 ml x 2). The collective organic phases were dried over anhydrous sodium sulphate and concentrated *in vacuo* to yield a reddish, thick liquid. This was vacuum-distilled to obtain the desired product in 78-80% yield (of theoretical), as a colourless liquid.

The whole process can be summarized as follows :

Substrate	Substrate in Ethanolic HCl	HCl Concn.	Temp	Time	Yield	Purity by HPLC
(R)-2-Hydroxy-4-phenylbutyronitrile	1 : 8 by volume	7-15% w/v	75-80°C	15 hrs	78-80% of theoretical	98%

Analytical data :

$^{20}[\alpha]_D$: -10° at 100% concentration (solvent free).

Reported $^{20}[\alpha]_D$: -10° ± 1 at 100% concentration (solvent free).

Boiling point : 125-127°C at 1mm Hg to 2 mm Hg vacuum; 120°C at 1.5 mm

NMR (Varian 60 MHz) : (CCl_4, TMS) 7.3 (s, 5 H), 3.8-4.3 (m, 3 H), 2.5 – 2.8 (t, 3 H), 1.4-2 (m, 2 H), 1-1.3 (t, 3 H)

Density : 1.0751

Refractive index : 1.502

HPLC 1. Column C_{18} (250 mm X 4.6 mm X 5 μ); mobile phase: methanol : H_2O (80 : 20); wavelength: 210 nm; flow rate: 1 ml/min; retention time: 4.17 minutes

HPLC 2. Column C_{10} Si 60 (5 μm) (250 mm X 4.0 mm X 5 μ); hexane : ethyl acetate(90 : 10); wavelength: 254 nm; flow rate: 1.0 ml/min; retention time: 21.60 minutes

IR: OH 3400 cm^{-1} – 3500 cm^{-1}; C=O 1750 cm^{-1}

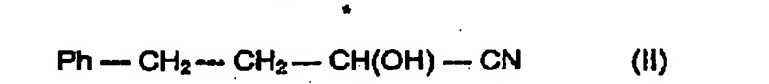
CLAIMS

1. A process for the stereospecific preparation of an ester of formula (I):

$$Ph - CH_2 - CH_2 - CH(OR^2) - COOR^1 \qquad (I)$$

wherein * signifies the (R) stereoisomer;
R^1 is selected from C_{1-6} alkyl, preferably ethyl; and
R^2 is hydrogen, a protecting group or a leaving group

which process comprises reaction of a nitrile of formula (II):



$$Ph - CH_2 - CH_2 - CH(OH) - CN \qquad (II)$$

wherein * signifies the (R) stereoisomer; and Ph is the phenyl group C_6H_5 with a solution of an inorganic acid in an alcohol.

2. A process according to claim 1, wherein the acid is hydrogen chloride (gas).

3. A process according to claim 1 or claim 2, wherein the alcohol is ethanol.

4. A process according to any preceding claim, wherein the reaction is carried out substantially in the absence of water.

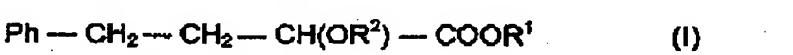
5. A process according to any preceding claim, wherein the acid/alcohol solution comprises >7% w/v of the acid (gas), based on the volume of the solution.

6. A process according to any preceding claim, wherein the reaction is carried out at the reflux temperature of the alcohol.

7. A process according to any preceding claim, wherein the reaction is carried out at 70-85 °C and goes to completion in the range of from 12 to 20 hours.

6. A process according to any preceding claim, wherein the ratio of nitrile of formula (II): acid/alcohol solution is in the range of from 1:6 to 1:10, preferably about 1:8, by volume.

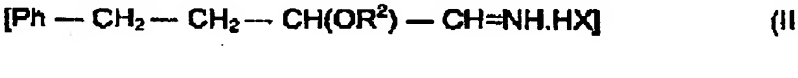
9. A process for the stereospecific preparation of an ester of formula (I):



$$Ph - CH_2 - CH_2 - CH(OR^2) - COOR^1 \quad (I)$$

wherein * signifies the (R) stereoisomer;
R^1 is selected from C_{1-6} alkyl, preferably ethyl; and
R^2 is hydrogen, a protecting group or a leaving group

which process comprises reaction of an intermediate imine of formula (III):



$$[Ph - CH_2 - CH_2 - CH(OR^2) - CH{=}NH.HX] \quad (III)$$

in which R^2 is as defined in formula (I); and X is the anion of an inorganic acid, such as halide, preferably chloride, with an alcohol of formula R^1OH, in which R^1 is as defined in formula (I)

10. A process according to claim 9, wherein R^1 is ethyl.

11. A process according to claim 9 or claim 10, wherein the reaction is carried out substantially in the absence of water.

12. An ester of formula (I), comprising at least about 97% of the (R) isomer, whenever prepared by a process according to any preceding claim.

ABSTRACT

SYNTHESIS OF CHIRAL INTERMEDIATES

A process for the stereospecific preparation of an ester of formula (I):

$$Ph — CH_2 — CH_2 — CH(OR^2) — COOR^1 \quad (I)$$

wherein * signifies the (R) stereoisomer;
R^1 is selected from C_{1-6} alkyl, preferably ethyl; and
R^2 is hydrogen, a protecting group or a leaving group

which process comprises reaction of a nitrile of formula (II):

$$Ph — CH_2 — CH_2 — CH(OH) — CN \quad (II)$$

wherein * signifies the (R) stereoisomer; and Ph is the phenyl group $C_6 H_5$ with a solution of an inorganic acid in an alcohol.